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Noninvasive Imaging of Prostate Cancer

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13. ABSTRACT (Maximum 200 Words) It is often impossible to optimally plan therapy for prostate cancer as current imaging is unreliable in determining if the cancer has spread beyond the prostate. Similarly, when prostate cancer recurs, as evidenced by a rising serum PSA level, non-invasively determining the precise location of the recurrence is often impossible. We have developed new radioactive compounds, NM404 and NM412, which are radioiodinated phospholipid ether analogs and have shown that they can localize to prostate cancer in rodent models of prostate cancer. We have recently shown that NM404 (I125 labeled) develops tumor uptake 37 times that of normal muscle, 9 times that of normal prostate and 3-11 times that of normal blood and liver, with 18% ID/g in the tumor at 5 days post injection. This level of targeting is considerably higher than most other radiopharmaceuticals. We also have completed pre clinical toxicology tests with the NM404 and NM412 reagents, which have shown no toxicity in doses up to 200 times that of the planned human dose in both rat and rabbit models. Dosimetry calculations for the radiolabeled compounds have been completed. These data have allowed for development of protocols to begin human imaging studies, after appropriate approvals are obtained.			
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FOREWORD

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Richard W. Smith 6/18/00

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Richard L. Wahl, M.D., PI

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5. INTRODUCTION:

Our laboratories have prepared and evaluated a number of radioiodinated phospholipid ether(PLE) analogs as candidates for the noninvasive imaging of human cancers. Several of these agents have been shown to selectively accumulate in a variety of animal tumors as well as human tumor xenografts. Moreover, preliminary results with one of the early candidates (NM-324) in cancer patients confirmed the ability of such agents to be taken up and retained by certain cancers. On the other hand, follow up studies in Copenhagen rats bearing Dunning R3327 prostate tumors and in SCID mice with PC3 xenografts showed NM-324 to be a poor candidate for visualizing prostate cancer. Therefore, major effort was undertaken to find agents better suited to imaging prostate cancer. Two of these newer agents, namely NM-404 and NM-412, were found to be significantly superior to NM-324 in both the rat and mouse tumor models. Moreover, lymphatic metastases were clearly delineated in the Dunning rat model. We believe NM-404 and NM-412 are excellent candidates for the diagnosis of prostate cancer and associated metastatic lesions and thereby warrant further preclinical and subsequent clinical evaluation.

6. BODY:

The overall hypothesis of our work is that radiolabeled phospholipid ether (PLE) analogs labeled with iodine will be safe and effective imaging agents in man. To prove this, their localization must first be shown to be effective in animals, toxicity data must be obtained in animals to show that the compounds are safe in these animals, dosimetry predictions based on biodistribution studies in animals must be performed and test of the unlabeled, and then subsequently the labeled compounds in man must be performed. These tasks are reflected in the statement of work of our original grant application.

Our work has been as follows: Synthesis of sufficient quantities of NM-404 for animal acute toxicology studies was planned. This has been accomplished. Sterile formulation of unlabeled NM-404 for toxicology, animal toxicology studies, and two animal species, analysis and report preparation has been accomplished. These show that NM-404 is safe in doses in excess of 200 fold the projected human dose. The preparation and purification of sterile formulations of I-125 labeled NM-404 for animal via distribution to imaging and dosimetry has been accomplished. The dosimetry has been reported at a recent scientific meeting (Zasadny et al, J Nucl Med). From these data it is possible to determine what dose would be appropriate in humans. The assessment of acute toxicity of unlabeled NM-404 in five normal male volunteers has not been performed, as approval and funding was granted initially only for the animal portion of the studies. This is planned in the next two months, following obtaining appropriate human study approvals. Preparation purification and sterile formulation of I-131 labeled NM-404 for patient evaluation has been done. Pilot labelings have been performed using an exchange reaction iodination of high efficiency. This is suitable for human labeling in our estimation. The administration of I-131 NM-404 to five patients with prostate cancer cannot be done until the normal volunteers studies are completed. Whole body imaging and dosimetric analysis will follow the human imaging with NM-404.

NM-412 has been synthesized for acute animal toxicology studies. Compound has been sent to a reference toxicology laboratory and NM-412 has been shown to be safe at 20% times the human dose in two animal species. A report has been generated indicating this from the reference toxicology laboratory. Thus, NM-412 has been prepared in sufficient quantity for human studies and has passed the safety tests. This was very recently completed. NM-412 has been radiolabeled and given to animals for biodistribution and dosimetry analysis. Targeting to animals with tumors has not yet been accomplished. Dosimetry calculations are underway. The assessment of unlabeled NM-412 in five normal volunteers has not yet been completed. This will follow performance of the study using cold NM-404 in normal volunteers. NM-404 and NM-412 labeling was sterile, and pure material has been obtained. Patient studies with NM-404 have not been completed and will follow the studies using unlabeled NM-404. Similarly, the NM-412 human studies are not yet completed as they will follow the NM-412 unlabeled human studies. We have not yet entered year 3 but believe we will achieve our overall aims as outlined in our statement of work, which would include giving NM-412 to patients for imaging and dosimetry and compiling these data for publication. Thus, the preclinical data necessary for initiation of the human studies has

been completed. Approvals from multiple committees for human studies are being sought and when these are obtained, approval from the Department of the Army will be requested to initiate the human studies, which would then progress rapidly.

The reviewers of this work are requested to see the appended material, specifically the report by Dr. Counsell and myself regarding the targeting of I-131 NM-404 in SCID mice bearing human PC-3 tumors. Table 1 of that publication shows the biodistribution at multiple time points. Striking is the high percentage injected dose per gram achieved in tumor and the high tumor to background ratios achieved compared to normal tissues with this agent. These, coupled with the excellent dosimetry (see abstract by Zasadny K, J Nucl Med attached) indicate that NM-404 is a very promising agent for our initial human trials. These animal targeting data and dosimetry data are essential as well as the toxicity data before our trial in humans can begin. However, we have successfully completed these milestones. Similar data shown soon be available within NM-412.

7. KEY RESEARCH ACCOMPLISHMENTS:

- Demonstration of lack of toxicity of NM-404 in relevant animal model systems at 200 fold projected human dose.
- Successful demonstration of lack of toxicity of NM-412 in same animal systems at comparable doses.
- Successful development of effective exchange radiolabeling method for NM-404 and NM-412 suitable for human dose preparation.
- Successful targeting of prostate cancer in PC-3 model with NM-404 with iodine label. Targeting to tumors is excellent indicating good probability of success in humans.
- Completion of dosimetric calculations indicating appropriate dose for administration to humans for NM-404.
- Completion of human protocol for submission to Radioactive Drug Research Committee, Institutional Review Board, Subcommittee on Human Use of Radioisotopes, Clinical Research Center, and pending these approvals to the U.S. Army Medical Research and Materiel Command before human studies begin.

8. REPORTABLE OUTCOMES:

Manuscripts, abstracts, presentations:

Counsell RE, Longino MA, Pinchuk Van Dort ME, Fisher SJ, Pinchuk AN, Skinner RWS, Zasadny KR and Wahl RL. Radioiodinated Phospholipid Ethers and Analogs as Tumor Imaging Agents. Fourth International Symposium on Radiohalogens, Whistler, B.C., Canada. September 9-13, 2000.

Counsell RE, Longino MA, Pinchuk AN, Skinner RWS, Fisher SJ, Van Dort ME, Pienta KF, and Wahl RL. Synthesis and Evaluation of a Radioiodinated Phospholipid Ether Analog (NM-404) for Diagnostic Imaging of Prostate Cancer. Third International Conference on Isotopes. September 1999

Zasadny KR, Longino MA, Fisher SJ, Counsell RE and Wahl RL. Predicted dosimetry for I-131 NM-404, a phospholipid ether agent for tumor imaging and possible therapy. J Nucl Med 40;1999:39p

9. CONCLUSIONS:

Excellent progress has been made toward our overall aim of evaluating I-131 NM-404 and I-131 NM-412 in humans as potential imaging agents for prostate cancer. Successful targeting in animals predicts successful targeting in people. Lack of toxicity in animal models at very high doses suggests the lack of toxicity in humans. Obviously, translation of this extensive pre-clinical data into humans is essential. This is the next step in our work. The targeting with NM-404 has been at such a high level that we believe there is potential for this to serve as a therapeutic as well as diagnostic for prostate cancer. For this reason, additional studies may be developed in the future with other methods of financial support to evaluate the therapeutic potential of phospholipid ether compounds. Satisfactory targeting to tumors in humans would need to be verified along with dosimetry before such predictions could suggest potential for therapy in humans.

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Counsell RE, Longino MA, Pinchuk Van Dort ME, Fisher SJ, Pinchuk AN, Skinner RWS, Zasadny KR and Wahl RL. Radioiodinated Phospholipid Ethers and Analogs as Tumor Imaging Agents. Fourth International Symposium on Radiohalogens, Whistler, B.C., Canada. September 9-13, 2000.

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Zasadny KR, Longino MA, Fisher SJ, Counsell RE and Wahl RL. Predicted dosimetry for I-131 NM-404, a phospholipid ether agent for tumor imaging and possible therapy. J Nucl Med 40;1999:39p

11. APPENDICES:

Counsell RE, Longino MA, Pinchuk Van Dort ME, Fisher SJ, Pinchuk AN, Skinner RWS, Zasadny KR and Wahl RL. Radioiodinated Phospholipid Ethers and Analogs as Tumor Imaging Agents. Fourth International Symposium on Radiohalogens, Whistler, B.C., Canada. September 9-13, 2000.

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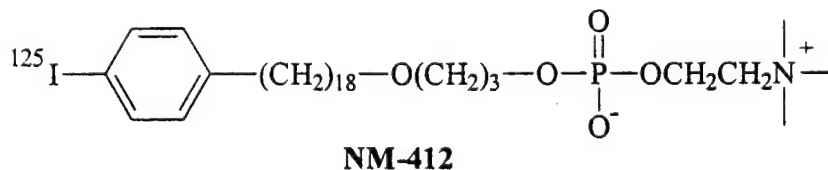
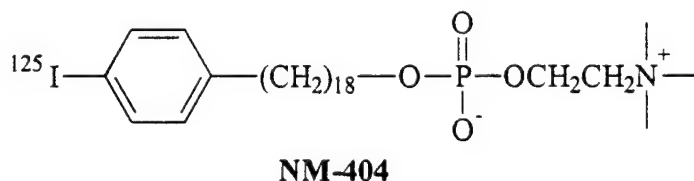
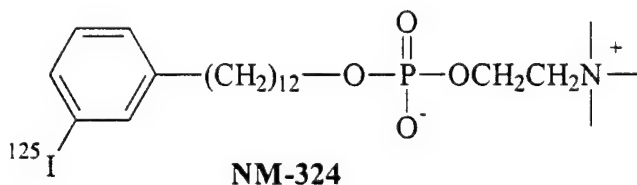
Zasadny KR, Longino MA, Fisher SJ, Counsell RE and Wahl RL. Predicted dosimetry for I-131 NM-404, a phospholipid ether agent for tumor imaging and possible therapy. J Nucl Med 40;1999:39p

Radioiodinated Phospholipid Ethers and Analogs as Tumor Imaging Agents

R.E. Counsell, M.A. Longino, M.E. Van Dort, S.J. Fisher, A.N. Pinchuk, R.W.S. Skinner,
K.R. Zasadny and R.L. Wahl.

Departments of Pharmacology, Radiology and Internal Medicine.
The University of Michigan Medical School, Ann Arbor, Michigan, 48109 U.S.A.

Based upon reports that human tumor tissue contains significantly higher levels of phospholipid ether (PLE) than adjacent normal tissue, our laboratory designed and synthesized a number of radioiodinated PLE analogs as potential tumor imaging agents. Several of these agents showed a striking ability to be taken up and retained by a variety of animal tumors and human tumor xenografts. In an effort to establish the relevance of our animal models to the human situation, one candidate (NM-324) was selected for further preclinical evaluation and subsequently studied in cancer patients. Such studies revealed that NM-324 was capable of imaging tumors in patients, but the high first pass clearance by the liver severely compromised its clinical utility as a diagnostic radioiopharmaceutical. Conversely, this study demonstrated that our animal models were appropriate for the identification of clinical candidates. Therefore, the design of second-generation candidates was focused on those that would possess a longer plasma half-life and/or more rapid metabolic clearance by the liver and other non-target tissues. Two animal models were employed for these studies, namely: SCID mice bearing 1) human lung adenocarcinomas (A549) and 2) human prostate cancer (PC-3). Based upon biodistribution and whole body imaging, two candidates (NM-404 and NM-412) were observed to be superior to NM-324. Moreover, toxicological analysis has shown both NM-404 and NM-412 to have no physiologic or pathologic effects in rats or rabbits at a dose significantly greater than 200 times the anticipated human dose. Phase I trials with both these agents in cancer patients are planned.



Synthesis and Evaluation of a Radioiodinated Phospholipid Ether Analog (NM-404) for Diagnostic Imaging of Prostate Cancer

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AND R.L. WAHL

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Imaging procedures play a major role in the current management of patients with prostate cancer. Despite advances in many of these procedures, improvements are still needed, especially in the area of Nuclear Medicine. The radioiodinated phospholipid ether analog (PLE) described here represents a new class of radiopharmaceutical, which has provided excellent images of prostate tumors in animal models and is now undergoing preclinical human pharmacokinetic evaluation.

Design and synthesis of radioiodinated PLE was based on the fact that various animal and human tumors contain higher concentrations of ether lipids than surrounding normal tissues. A number of radioiodinated PLE were synthesized and evaluated by γ -camera imaging using rat tumor models as well as nude and SCID mice bearing human tumor xenografts. Of the several agents that displayed promising results, one candidate (NM-324) was selected for further preclinical evaluation and subsequently studied in cancer patients in an effort to ascertain its ability to be retained in human tumors. These studies revealed that NM-324 was capable of imaging tumors in patients, but the high first pass clearance by the liver severely compromised its clinical utility as a diagnostic radiopharmaceutical. Conversely, this study demonstrated that our animal models were appropriate for the identification of clinical candidates.

In an effort to obtain a more suitable clinical candidate, the present study undertook the synthesis and evaluation of additional radioiodinated PLE with a focus on those displaying good tumor avidity and a prolonged plasma half-life relative to the prototype. Biodistribution analysis and γ -camera imaging of Copenhagen rats bearing Dunning R3327 prostate tumors and SCID mice bearing human prostate cancer (PC-3) revealed NM-404 to display a longer plasma half-life, better tumor/liver and tumor/kidney ratios, and significantly superior imaging properties than the initial prototype, NM-324. (Supported by the U. S. Department of Defense grant DAMD17-98-1-8528 and the SPORC in Prostate Cancer grant P50 CA 65968)

In the late 1960's, Snyder and coworkers [1] performed a series of experiments designed to evaluate the lipid composition of normal and neoplastic tissues. They found that both animal and human tumor tissue contained much larger quantities of naturally-occurring ether lipids relative to corresponding normal tissues. This biochemical difference between normal tissues and cancer suggested to us that appropriately structured ether lipids might serve as carriers for targeting radioiodine to human tumors. In this regard, we previously described the remarkable capacity of certain radioiodinated phospholipid ether (PLE) analogs to be selectively retained by a variety of rodent and human tumor cell lines [2]. Moreover, this property made it possible to obtain images of these tumors in rabbits, rats and mice using γ -camera scintigraphy.

Based on these and other preliminary results, one of these radioiodinated analogs, 12-(*m*-iodophenyl)dodecyl phosphocholine (NM-324, Figure 1), was approved for pharmacokinetic evaluation in human cancer patients in order to determine whether the results in animals could be confirmed in humans. Although high first pass clearance by the liver compromised the imaging capabilities of NM-324, imaging of the tumors was successful in several patients, and thereby confirmed the potential of radioiodinated PLE analogs for tumor imaging in patients [3].

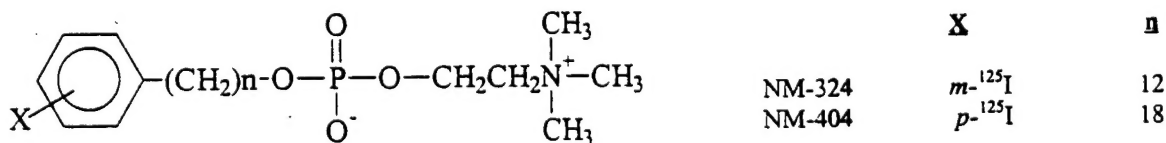
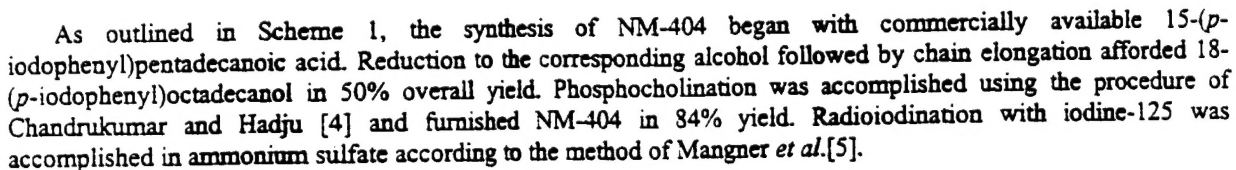


Figure 1. Structures for NM-324 & 404.

Scheme 1. Synthesis of NM 404



Based on these results, NM-404 was selected for further preclinical analysis. The Toxicology Research Center at the University Buffalo found an isotonic solution of stable NM-404 to have no physiologic or pathologic effects in rats or rabbits at a dose 200 times the anticipated human dose. Moreover, the above tissue distribution studies along with those in normal Sprague-Dawley rats predicted that ^{131}I labeled NM-404 could be safely injected in humans with thyroid blocking at a dose of 2 mCi.[6]. Phase I studies in humans are planned.

Table 1. Biodistribution of ¹²⁵I-NM-404 in male SCID mice bearing PC-3 human prostate cancer xenografts, expressed as Dose/gm \pm SEM and Target/Non-target Ratio. (n=4)

	1 Day	3 Day	5 Day	8 Day
Tissue	% Dose/gm (Tumor/Tissue)	% Dose/gm (Tumor/Tissue)	% Dose/gm (Tumor/Tissue)	% Dose/gm (Tumor/Tissue)
Blood	5.74 \pm 0.20 (1.59)	3.10 \pm 0.13 (4.24)	3.08 \pm 0.09 (5.87)	2.17 \pm 0.07 (6.91)
Kidney	4.22 \pm 0.14 (2.17)	2.14 \pm 0.11 (6.13)	2.28 \pm 0.09 (7.92)	1.46 \pm 0.04 (10.26)
Liver	3.69 \pm 0.21 (2.48)	1.93 \pm 0.10 (6.81)	1.63 \pm 0.06 (11.07)	1.02 \pm 0.06 (14.69)
Lung	5.36 \pm 0.33 (1.71)	2.60 \pm 0.20 (5.06)	2.27 \pm 0.09 (7.97)	1.54 \pm 0.06 (9.70)
Muscle	0.79 \pm 0.03 (11.50)	0.57 \pm 0.04 (22.98)	0.49 \pm 0.03 (36.95)	0.40 \pm 0.03 (37.33)
Prostate	2.60 \pm 0.15 (3.51)	1.40 \pm 0.27 (9.40)	1.96 \pm 0.25 (9.20)	1.41 \pm 0.06 (10.64)
Tumor	9.14 \pm 0.69 (1.00)	13.14 \pm 0.40 (1.00)	18.06 \pm 0.80 (1.00)	14.96 \pm 0.63 (1.00)

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6. Zasadny K. R., Longino M. A., Fisher S. J., Counsell R. E. and Wahl R. L., Predicted dosimetry for I-131-NM-404, a phospholipid ether agent for tumor imaging and possible therapy, *J. Nucl. Med.* **40** (1999) p. 39P.

Radiopharmaceutical Chemistry Track Dosimetry: Clinical Dosimetry

2:15 PM-3:45 PM Session 23

Room: 403 B

Moderator: Barry W. Wessels, PhD
Co-Moderator: John L. Humm, PhD

No. 155

PREDICTED DOSIMETRY FOR I-131-NM-404, A PHOSPHOLIPID ETHER AGENT FOR TUMOR IMAGING AND POSSIBLE THERAPY. K. R. Zasadny*, M. A. Longino, S. J. Fisher, R. E. Counsell, R. L. Wahl, The University of Michigan Medical Center, Ann Arbor, MI. (500384)

Objectives: Phospholipid ether agents have the potential to image and possibly deliver therapeutic radiation to a wide variety of human tumors due to their differentially slower metabolism in tumors relative to normal tissues. Previous phospholipid ether agents have successfully targeted a variety of human neoplasms including colon, lung and ovarian cancer. Iodine-labeled NM-404 has successfully targeted tumors in the rat including the Walker256 tumor line. This study focuses on predicted normal organ dosimetry for I-131-labeled NM-404 for humans based on biodistribution studies in the rat. **Methods:** Tissue distribution studies were carried out after I-125-labeled NM-404 injection in male Sprague-Dawley rats at six time points (3 animals per time point): 1 hr, 6 hr, 24 hr, 72 hr, 7 d and 10 d post injection. Kg*%ID/g uptake in tissues were calculated. Time-activity curves were fit by non-linear least-squares regression using a biexponential model. Extrapolation to human was accomplished by scaling by the total body and organ masses of the MIRD reference adult phantom. Fit time-activity curves were corrected for I-131 decay and integrated to determine dosimetric residence times for the following source organs: adrenals, heart, kidneys, liver, lungs, muscle, marrow, spleen, testes and thyroid (unblocked). The MIRDOSE 3.1 program was used to produce dose estimates. **Results:** The NM-404 pharmacokinetics show a rapid clearance from the blood followed by a long-lived component. Normal tissues generally show rapid uptake followed by slow clearance. Highest normal organ dose estimates (mGy/MBq) for I-131-labeled NM-404 for the reference adult were seen in thyroid (unblocked) (0.82), followed by adrenals (0.61), lungs (0.56), kidneys (0.50), spleen (0.41), testes (0.39) and liver (0.34). The dose-limiting organ is the testes, with a 3 cGy dose resulting from a 78 MBq administration. **Conclusion:** Predicted I-131-labeled NM-404 dosimetry results indicate clinically-useful activities for imaging may safely be injected in humans with thyroid blocking. Phase I studies in humans are planned using a 74 MBq (2 mCi) dose.

No. 156

OPTIMIZING COMBINATION THERAPY WITH RADIOLABELED ANTIBODIES AND EXTERNAL BEAM. J. L. Humm*, S. Ruan, S. M. Larson, J. A. O'Donoghue, Memorial Sloan-Kettering Cancer Center, New York, NY. (100338)

Objective: To determine the optimum sequence for combined modality therapy with radiolabeled antibodies and fractionated external beam. **Methods:** The uptake and distribution of I-131 labeled tumor specific A33 monoclonal antibody was determined in SW1222 human colon carcinoma xenografts in nude mice for four study groups (4 animals per group): (1) radiolabeled antibody alone, i.e. pre-radiation therapy controls, (2) antibody administered (day 0) immediately prior to the first of five 2 Gy daily fractions of 320 kVp X-rays, (3) antibody administered after the 5th radiation fraction (day 5), (4) antibody administered five days post irradiation (on day 10). Tumors were excised 5 days post antibody administration. The %injected dose per gram was calculated. Tumors were frozen and sectioned for histology and phosphor imaging autoradiography. The percentage of antigen expressing cells was measured by immunohistochemistry. **Results:** The average tumor uptake relative to control group 1 were 1.47 (group 2), 0.78 (group 3) and 0.21 (group 4) respectively. This illustrates that tumor uptake is increased by almost 50% when the antibody is present in blood at the start of irradiation. 5 days into a fractionated irradiation protocol, antibody uptake was reduced, falling more significantly on day 10. Autoradiographs demonstrated decreased uptake uniformity for

groups 3 and 4. Immunohistochemistry showed a reduction in A33 antigen positive cells from 85, 64, 50 to 41% for groups 1-4 respectively. **Conclusions:** Radioimmunotherapy should be administered just prior to the initiation of a course of external beam for maximum tumor uptake and radiolabeled antibody dose. Radiation therapy appears to cause a transient increase in capillary leakage to macromolecules, followed by a reduction at later times possibly the result of capillary damage and occlusion.

No. 157

NEW ADDITIONAL MIRD MODEL BASED ADULT PHANTOMS OF DIFFERENT SIZE FOR INTERNAL DOSIMETRY IMPROVEMENT. I. Clairand*, M. Ricard, M. Durigon, M. Di Paola, B. Aubert, Institut Gustave-Roussy, Villejuif, France; Institut Gustave-Roussy and U494 INSERM, Villejuif, France; Hopital Raymond-Poincaré, Garches, France. (500325)

Objectives: In internal dosimetry, patient morphology is represented by a limited number of models. In the MIRD schema, the adult male phantom is an individual measuring 1.74 m and weighing 70 kg, the adult female is represented by 1.64 m and 58 kg. In order to work with more realistic models, we defined additional MIRD based mathematical anthropomorphic phantoms which represent the physical differences encountered in the adult population. The influence of these morphologic variations on the S-factors was studied. **Methods:** The analysis of anthropometric data gathered from a legal medicine department (355 men and 329 women of Caucasian type) showed that the mass of most organs is statistically correlated with the height of the body. This led us to develop 3 mathematical male phantoms of 1.60 m, 1.70 m and 1.80 m and 3 female phantoms of 1.50 m, 1.60 m and 1.70 m. These phantoms were built using combinatorial geometry. The S-factors for all the usual target organs were then calculated using a home made Usercode DOSE3D based on the EGS4 Monte Carlo code, when I-131 is uniformly distributed in the stomach and the urinary bladder. **Results:** An increase in the phantom height by 10 cm leads to a mean S-factor reduction by 20 % when the stomach is the source organ and by 29 % in the case of the urinary bladder. When the phantom height increase is 20 cm, the values are 35 % and 48 %. In some cases, especially when the target organ is far away from the source organ, the differences are 4 fold or more. **Conclusion:** This work showed the influence of the morphology on the S-factors. The development of new mathematical adult phantoms should contribute to improve dosimetric estimations by taking into account more realistic geometric parameters.

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ERROR ANALYSIS OF GAMMA CAMERA BASED DOSIMETRY IN RADIOIMMUNOTHERAPY. K. A. Hamacher*, G. Sgouros, Memorial Sloan-Kettering Cancer Center, New York, NY. (100032)

Objectives: The aim of the work presented here was to implement a detailed method to evaluate the error associated with the calculation of the absorbed dose to normal organs in patients undergoing radioimmunotherapy. **Methods:** The overall uncertainty in absorbed dose is assumed to include errors in (1) estimation of organ activity at multiple time-points from radionuclide imaging and (2) estimation of organ volume. Organ activity quantification is comprised of the following measurements, each of which will have its own uncertainty: attenuation correction, scatter correction, camera calibration, selection of an appropriate background region-of-interest, and selection of a region-of-interest for the organ. Several of these measurements are comprised of a number of independent measurements which themselves are subject to uncertainty. The uncertainty in organ volume quantification will be highly dependent upon the technique used to estimate organ volume with CT or MRI-based measurements being the most accurate and estimation based upon nuclear medicine imaging being less accurate. Error values were assigned to each of the measurements identified above and then propagated to obtain the uncertainty in calculated absorbed dose. Uncertainties were calculated assuming dosimetry was based upon imaging In-111, I-131, or Bi-213. Uncertainty values were determined for volume estimates based upon CT/MRI, SPECT and also estimates based upon organ projections obtained from planar imaging. **Results and Conclusion:** A formalism has been established which provides the uncertainty associated with conventional absorbed dose calculations. This analysis makes it possible to quantitatively identify those elements that contribute the largest uncertainty to absorbed dose estimates, thereby pointing to areas where improvement would be most beneficial.